

Phages like these studding an *Escherichia coli* bacterium target specific bacteria, complicating their use in medicine.

at UCSD: AmpliPhi and Adaptive Phage Therapeutics (APT), based in Gaithersburg, Maryland, which has licensed the Navy's phage collection.

Running phages through modern clinical testing has proved difficult in the past. A European Union-sponsored trial known as PhagoBurn was all but derailed by a series of setbacks (*Science*, 24 June 2016, p. 1506). "It was not an ideal trial, let me say it like that," says Jean-Paul Pirnay, a bioengineer at Queen Astrid Military Hospital in Brussels, one of the partners in PhagoBurn. A key obstacle was the fact that the trial targeted burn wounds, which often harbor multiple bacterial infections. That made it hard to test the effects of a phage therapy aimed at just one species. Designed to include 220 patients, the trial ultimately recruited only 27, and it has not yet published its results.

The anticipated trials at UCSD, on the other hand, will focus on patients with a single, known bacterial infection, Schooley says. But he admits it will still be tricky to design trials that isolate the effect of phages without withholding other potentially beneficial treatments, including antibiotics. (Ultimately, Schooley and many others expect phages to work in tandem with antibiotics—not to replace them.)

IPATH collaborators will also have to navigate a drug approval system suited to more conventional treatments. Because a phage cocktail will often have to be custom-designed for an individual, regulatory agencies may not have a single product to evaluate for safety and efficacy. But after initial talks with FDA, Greg Merrill, APT's CEO, is confident the agency will be flexible. He plans to seek approval for an entire library of phages—about 100 for each bacterial species—from which doctors could create a cocktail of one to five phages for a patient.

In the meantime, Strathdee says the UCSD team plans to keep securing phages for individual cases under FDA's emergency pathway. She and Schooley already get several inquiries a week from patients and families fighting drug-resistant infections. "We hope to not send people with superbugs away, but to welcome them with open arms," she says. "Right now, they don't have anywhere to go."

Pirnay, whose team finds and formulates phages to treat infections related to battlefield injuries, has a piece of advice for the UCSD group: "Be careful not to create too high an expectancy with the public," he says. "Even when you do not say that you will be able to treat everything, you create a demand with desperate patients." ■

PUBLIC HEALTH

Reports of inner-ear damage deepen diplomat controversy

As mystery symptoms reported in Cuba spread to China, some blame an attack; others see "suggestion and paranoia"

By Richard Stone

The mystery began late in 2016. Personnel attached to the U.S. embassy in Havana developed symptoms such as headaches, dizziness, and insomnia after hearing strange loud sounds or feeling a sensation of pressure. Since then, dozens of diplomats have been withdrawn from Cuba, and international tensions have risen. This month, the mystery spread, with reports from the U.S. Department of State that "a number" of diplomats at its consulate in Guangzhou, China, had been flown home with symptoms similar to those reported in Cuba—where two more diplomats have reportedly fallen ill. Yet 18 months in, an explanation is nowhere in sight, although hypotheses have proliferated.

Former Secretary of State Rex Tillerson blamed a deliberate "health attack" for the Cuba ailments, whereas some neuroscientists and psychologists—and a panel of Cuban scientists—have written them off as the result of stress. Some unaffected diplomats from the Havana embassy agree. "There was a perfect storm of suggestion and paranoia," one told *Science*, speaking on condition of anonymity.

But a few researchers are finding hints of a physical cause. In February, a team at the University of Pennsylvania described neurological deficits in embassy personnel who had reported symptoms. And in unpublished results, Michael Hoffer, an otolaryngologist at the University of Miami in Florida, and his colleagues describe a unique vestibular and cognitive disorder in two dozen people evacuated from the Havana embassy. They believe some kind of directed energy device may have caused inner-ear damage.

Taking both teams' observations together, "It seems like something's going on," says Lee Goldstein of Boston University, who studies neurodegenerative diseases. But, he adds, "We're still very much in the early days of trying to figure this out."

The first to fall ill was a U.S. intelligence agent in Havana. The "index case," as Hoffer calls him, complained to the embassy doctor of ear pain, tinnitus, vertigo, and feeling "cognitively not perfect." The agent said he had heard "a really odd, loud

noise that seemed to follow him in the room," says Hoffer, who examined him in February. "When he opened the front door, the sound went away." Other U.S. personnel reported similar symptoms.

At the end of March 2017, recalls the U.S. diplomat who spoke with *Science*, then-Ambassador Jeffrey DeLaurentis summoned personnel with security clearances—about 30 in all—for a classified briefing in a special installation in the embassy: a steel conex box suspended on pylons that's shielded from surveillance. The "working hypothesis," the diplomat says, was the victims were being targeted by a long-range acoustic device. Embassy security officers advised their colleagues to record harassing sounds and



Most personnel have been evacuated from the U.S. embassy in Havana, leaving only a skeleton crew.

report any symptoms. In April 2017, the embassy clued in all members of its diplomatic corps and advised people to sleep in the middle of a room, away from windows.

"Everybody was in a frenzy about it," says a second U.S. diplomat who was stationed in Havana at the time with young children. "We had a big window in the front of the house. It was a horrible feeling. We just thought, 'Oh my God, we're in harm's way,'" she says. "You start to feel paranoid."

Hoffer, a former military doctor who had treated concussion victims in Iraq, was enlisted to assess the ailing diplomats. His team had been working on better tests for concussion in athletes, together with University of Miami neurophysiologist Bonnie

Levin, otolaryngologist Carey Balaban of the University of Pittsburgh in Pennsylvania, and engineers at Neuro Kinetics, Inc., also in Pittsburgh. In one test, the patient wears goggles that project a moving field of light points while a camera observes eye movements. In healthy subjects, the eyes reflexively track the lights. People with a head injury are often unable to focus on them at all. The goggles can also perform other eye movement tests sensitive to concussions.

Hoffer and colleagues tested several dozen Havana embassy personnel who had been flown to Miami. About half flunked a critical eye movement test, and more than two dozen reported dizziness or vertigo. In those individuals, Balaban says, further tests implicated damage to the ear's otolith organs, the utricle and the saccule, key to sensing gravity. "That's prima facie evidence the diplomats are not making this up," Hoffer says.

"I agree with that," Goldstein says, but he is skeptical of speculation about what might be causing the injuries. Balaban and his colleagues venture that a directed energy source could have damaged the exquisitely sensitive utricle and saccule. Maintaining balance became so taxing, they say, that victims reported concussionlike symptoms, finding it hard to think and concentrate. Hoffer acknowledges, however, that some patients may have had preexisting injuries. One had been stationed in Afghanistan and may have been exposed to a blast there. (His team's findings are under review at a medical journal, he says.)

In January, after an investigation that included fieldwork in Havana, the Federal Bureau of Investigation found no evidence for an attack with powerful energy beams. But the Department of Defense is giving the possibility a closer look. U.S. Navy acoustic expert Kurt Yankaskas, who runs the noise-induced hearing loss program at the Office of Naval Research in Arlington, Virginia, thinks an energy weapon is a possibility, although "it would have to have been tight-beamed and high frequency." One candidate, he says, is so-called hypersonic sound, generated by the interference of ultrasonic waves, which the Navy has evaluated as a means of communicating on deafening aircraft carrier decks.

Whatever the symptoms' cause, only a minority of embassy staff were stricken. The Department of State dispatched Hoffer and University of Miami physical therapist James Buskirk to Havana in April 2017 to perform tests on several dozen of the remaining personnel. "A lot of people at the embassy wanted reassurance they weren't affected," Buskirk says. None had experienced symptoms, and they all scored normally on the tests.

Other researchers and physicians maintain that mass psychogenic illness could explain some, if not all, of the symptoms. A panel of

Sounds and fury

A mystery illness among U.S. diplomats in Cuba and China has raised international tensions and sparked debate about possible causes.



Cuban scientists that evaluated U.S. evidence and gathered its own data concluded in December 2017 that U.S. recordings of a grating, supposedly unnatural sound match the chirping of the Jamaican field cricket, a notoriously noisy insect that's common in Cuba (*Science*, 8 December 2017, p. 1236). People's state of mind determined whether they developed symptoms, the first diplomat asserts. "I don't know anybody who at one point thought we were under no risk and then subsequently decided that they were a victim."

He himself heard a mysterious sound one night last June. "Standing in the atrium of my house, it was so loud and metallic, my brain literally hurt," he says. He called the embassy security officer, who came over and recorded the sound. But his housekeeper knew right away it was a Jamaican field cricket. "She grew up on a farm. She's like, 'Oh yeah, they drive people crazy.'"

The second diplomat echoes that experience. The sound, she says, "was eerie. A really nasty sound. Not like your head is going to explode, but it's very unpleasant." Then she and her family heard it on several more occasions outdoors. "That was reassuring. We realized it had to be the crickets."

She acknowledges that over time, a divide widened between "the true believers" and those like her who are skeptical that there was an attack. At the same time, she says, she's open-minded to plausible explanations for the mystery illness.

Both U.S. and Cuban authorities are struggling to provide them. On 5 June, Secretary of State Mike Pompeo announced the creation of a task force that will lead an interagency probe. And earlier this month, the president of the Cuban Academy of Sciences (ACC) in Havana, neurophysiologist Luis Velázquez Pérez, proposed that ACC and the U.S. National Academy of Sciences (NAS) in Washington, D.C., team up to try to solve the mystery. (A spokesperson for NAS could not comment on whether it will respond.) John Van Horn, a neuroscientist at the University of Southern California in Los Angeles, hopes the research will go forward. "Opened and reasoned scientific scrutiny of these cases" is needed, he says, "to reach a more precise conclusion than that some evil boogeyman has developed a supersecret sound gun and is using it specifically against foreign diplomats."

"I have every incentive to know the truth," the second diplomat says. "It's in our best interest to know if there's something that could damage us or our kids." ■

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Science **360** (6395), 1281-1282.
DOI: 10.1126/science.360.6395.1281

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